

Correspondence

Treatment of cutaneous chronic graft-versus-host disease with topical pimecrolimus

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A 48-year-old woman had undergone allogeneic SCT for B-cell CLL. GVHD prophylaxis comprised cyclosporine, mycopenolate mofetil and prednisolone for 3 months. Cutaneous chronic GVHD involving the face appeared a year after HSCT with scaling, reddish, pruritic plaques in the seborrhic areas (Figure 1a). No other areas of the skin, mucosa or nails were affected. The differential diagnosis included eczema, seborrhic dermatitis, and fungal and bacterial infections. A punch biopsy of the affected skin showed lichenoid chronic GVHD. Histologically, there was partial epidermal atrophy with hyperkeratosis and hypergranulosis. There was focal vacuolar alteration of the basal layer with individual necrotic keratinocytes with eosinophilic cytoplasm without pyknotic nuclei (bolloid bodies) in the epidermal layer. Below these changes, there was a focal lichenoid-organized lymphohistiocytic infiltration with melanophages. Abdominal ultrasound and laboratory investigations (including electrolytes, complete blood count, liver enzymes and renal function) were normal. Given the history and clinical findings, the chronic GVHD was diagnosed.

We treated our patient with topical pimecrolimus 1% cream (Douglan[®]) twice daily for 2 months. No systemic immunosuppression was used. The patient responded very

well to this therapy showing complete resolution of pruritus and the lesions (Figure 1b). She has been free of chronic GVHD for 13 months following topical pimecrolimus.

Acute and chronic forms of cutaneous GVHD show various manifestations including exanthema, erythrodermia and toxic epidermal necrolysis as acute reactions, and lichenoid or sclerodermatous changes as chronic reactions.¹ The mainstay of the treatment of chronic GVHD is systemic immunosuppression with opportunistic infections being a major adverse effect. However, cutaneous chronic GVHD may also respond to topical therapy.²

Topical tacrolimus has been shown to be effective drug in treating chronic skin GVHD.^{3,4} Pimecrolimus, an ascomycin derivative, is a new immunomodulating macrolactam like tacrolimus, and was specifically developed for the treatment of inflammatory skin diseases. The interest in pimecrolimus has been substantial due to its significant anti-inflammatory and immunomodulatory activity coupled with its low systemic immunosuppressive potential. It acts by blocking T-cell activation.⁵

Pimecrolimus (like all ascomycins) is an immunophilin ligand, which binds specifically to the cytosolic receptor, immunophilin macrophilin-12. This pimecrolimus-macrophilin complex effectively inhibits the protein phosphatase calcineurin, by preventing calcineurin from dephosphorylating the nuclear factor of activated T cells (NF-AT), a transcription factor. This results in the blockage of signal transduction pathways in T cells and the inhibition of the synthesis of inflammatory cytokines, specifically Th1- and Th2-type cytokines.⁵ Pimecrolimus has also been shown to prevent the release of cytokines and proinflammatory mediators from mast cells. In animal models of allergic



Figure 1 (a) Cutaneous chronic GvHD 1 year after HSCT. (b) Resolution of GVHD after 2 months of topical pimecrolimus therapy.

contact dermatitis, topical pimecrolimus was found to be effective. In human placebo-controlled studies in patients with allergic contact dermatitis, pimecrolimus has demonstrated significant efficacy.⁶

The efficacy of pimecrolimus cream was comparable to betamethasone valerate;⁵ however, pimecrolimus was not associated with any of the characteristic side effects of steroids like skin atrophy. Our data suggest that topical pimecrolimus could be effective in skin GVHD, and may be particularly attractive for use in areas such as the face where visible atrophic changes would be highly undesirable.

T Schmook¹
J Kraft³
B Benninghoff²
I Nindl¹
J Roewert¹
C Ulrich¹
E Stockfleth¹

¹*Department of Dermatology
(Skin Cancer Center
Charité), Charité, University
Hospital Berlin, Germany;*
²*3M Medica, Neuss,
Germany; and*
³*Faculty of Medicine, University
of Toronto, Toronto,
Canada*

References

- 1 Ferrara JL, Cooke KR, Teshima T. The pathophysiology of acute graft-versus-host disease. *Int J Hematol* 2003; **78**: 181–187.
- 2 Higman MA, Vogelsang GB. Chronic graft versus host disease. *Br J Haematol* 2004; **125**: 435–454.
- 3 Choi CJ, Nghiem P. Tacrolimus ointment in the treatment of chronic cutaneous graft-vs-host disease: a case series of 18 patients. *Arch Dermatol* 2004; **137**: 1202–1206.
- 4 Elad S, Or R, Resnick I, Shapira MY. Topical tacrolimus – a novel treatment alternative for cutaneous chronic graft-versus-host disease. *Transplant Int* 2003; **16**: 665–670.
- 5 Gupta AK, Chow M. Pimecrolimus: a review. *J Eur Acad Dermatol Venereol* 2003; **17**: 493–503.
- 6 Alomar A, Berth-Jones J, Bos JD *et al.* European Working Group on Atopic Dermatitis. The role of topical calcineurin inhibitors in atopic dermatitis. *Br J Dermatol* 2004; **151** (Suppl. 70): 3–27.